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Lactone Carboxylic Acids. VII. Reaction of Lactone Pyrazolines with Acetic Anhydride. A Preparation of Lignans Skeleton by Thermal Decomposition of Pyrazoline

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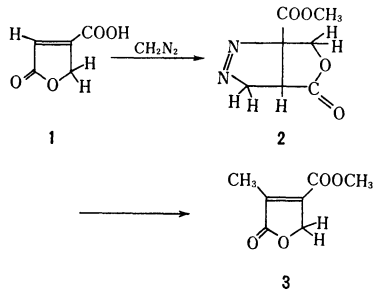
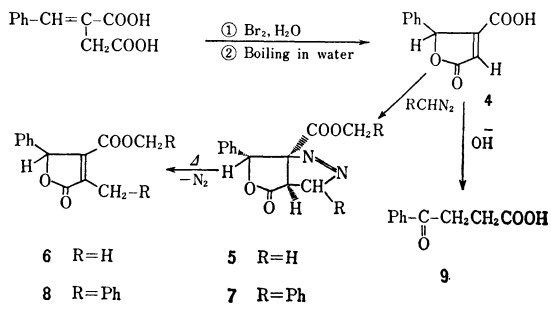
Cycloaddition of diazomethanes to aconic acids (**4** and **14**) gave 1-pyrazolines (**5**, **7** and **15**). Thermal decomposition of **7** afforded γ-phenyl-α-benzylaconic acid **8** having a lignans skeleton. By the action of phosphoric acid **5** was converted into 2-pyrazoline **12**. The chemical nature of pyrazolines (**5** and **12**) is discriminated by treatment with acetic anhydride in the presence of *p*-toluenesulfonic acid. Thus, 1-pyrazoline **5** gave the corresponding derivatives (**10**, **11** and **13**), and **12** gave **13**. The thermochemical stability of the pyrazolines (**15** and **16**) were also studied. A possible mechanism of the formation of **10** and **13** is described.

In the preceding paper of this series, the synthesis of γ-butyrolactones having lignans skeleton was reported.[1] The present paper describes an alternative route to ligans-like compounds and some new properties of pyrazoline derivatives[2] obtained by the addition of diazomethanes to aconic acid (**4** and **13**).



1 **2** **3**

The reaction of aconic acid **1** with diazomethane gives the corresponding pyrazoline **2** which undergoes thermal decomposition to afford **3**.[3] The applicable mode of cycloaddition of diazomethane to aconic acid has led to an extensive study on the preparation of lignans.[4] γ-Phenylaconic acid **4**, obtained in good yield by treatment of α-benzylidenesuccinic acid[5] with bromine in water followed by hot water, was characterized by the absorption spectrum: 1733 (carbonyl $\nu_{C=O}$) and 1645 cm^{-1} and by hydrolysis[6] with alkali to γ-keto acid **9**.[7]



6 R=H **5** R=H **9**

8 R=Ph **7** R=Ph

Scheme I

The adduct[8] of **4** with diazomethane gave **6** in a quantitative yield, when heated at 145°C for 30 min. Similarly, phenyldiazomethane[9] in the same reaction yielded crystalline pyrazoline **7** which was subjected to thermal decomposition to give **8**. The structural assignment of **8** was carried out by the infrared and NMR spectra which revealed the pres-

1) A. Takeda and S. Torii, This Bulletin, **41**, 1468 (1968).

2) See Reviews "Cycloaddition of Diazoalkanes," A. Ohta, *Yuki Gosei Kagaku Kyokai Shi*, **26**, 115 (1968).

3) R. F. Rekker, J. P. Brombacher and W. Th. Nauta, *Rec. trav. chim. Pays-Bas*, **73**, 417 (1954).

4) W. M. Hearon and W. S. MacGregor, *Chem. Rev.*, **55**, 957 (1955); F. M. Dean, "Naturally-occurring Oxygen Ring Compounds," Butterworths, London (1963), p. 29.

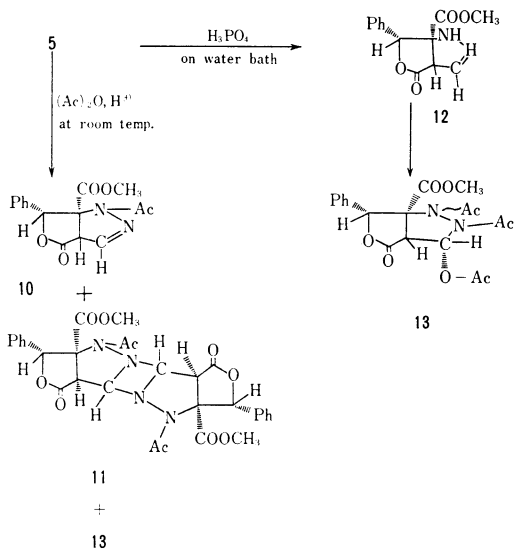
5) H. J. Bestmann and H. Schulz, *Chem. Ber.*, **95**, 2921 (1962).

6) A. Takeda, K. Takahasi, S. Torii and T. Moriwake, *J. Org. Chem.*, **31**, 616 (1966).

7) L. F. Somerville and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, p. 81 (1943).

8) It is expected that considering the Stuart model of **4** the bulkiness of the phenyl group provides a back side attack of diazomethane. Selective decomposition of these kinds of adducts to the corresponding unsaturated compounds such as **6** and **8** has been reported: *e.g.*, a) J. Hamelin, *C. R. Acad. Sci., Paris, Ser.* c, **261**, 4776 (1965); b) J. Hamelin and R. Carrie, *ibid.*, **261**, 5545 (1965).

9) R. J. Mohrbacher and N. H. Cromwell, *J. Amer. Chem. Soc.*, **79**, 401 (1957).



Scheme II

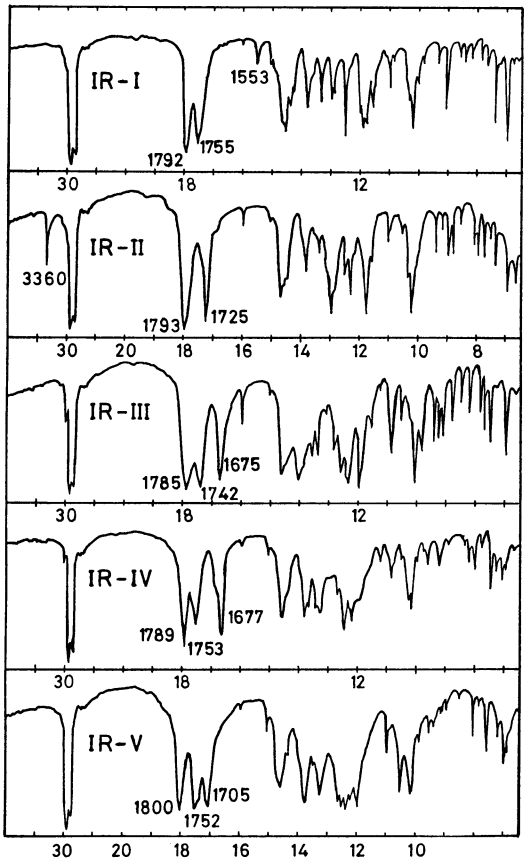


Fig. 1. IR spectra of the key compounds are as follows: IR-I, methyl γ-phenyl-α,β-(1-pyrazolino)-paraconate **5**; IR-II, methyl γ-phenyl-α,β-(2-pyrazolino)paraconate **12**; IR-III, *N*-Acetyl-2-pyrazoline **10**; IR-IV, Dimer of **10**; IR-V, the compound **13**.

ence of lactone, ester and double bond functions, 1785, 1725 and 1670 (shoulder) cm^{-1}, respectively, and also the presence of two kinds of methylene group (C=C-CH_2-Ph, τ 7.00, q, and -O-CH_2-Ph 5.03, q).

Many papers concerning cycloaddition of diazoalkanes to suitable unsaturated compounds have recently appeared.[2,10] However, concerning the isolation of the products, it was difficult to obtain the tautomers concurrently,[11] *i. e.*, 1-prazolines and 2-pyrazolines,[2] and the reactivities of these tautomers have not yet been examined. 2-Pyrazolines **12**, readily obtained by the treatment of **5** with phosphoric acid[12] at 70—80°C, can be distinguished by its infrared spectrum as shown in Fig. 1, since instead of the absorption band at 1553 cm^{-1} due

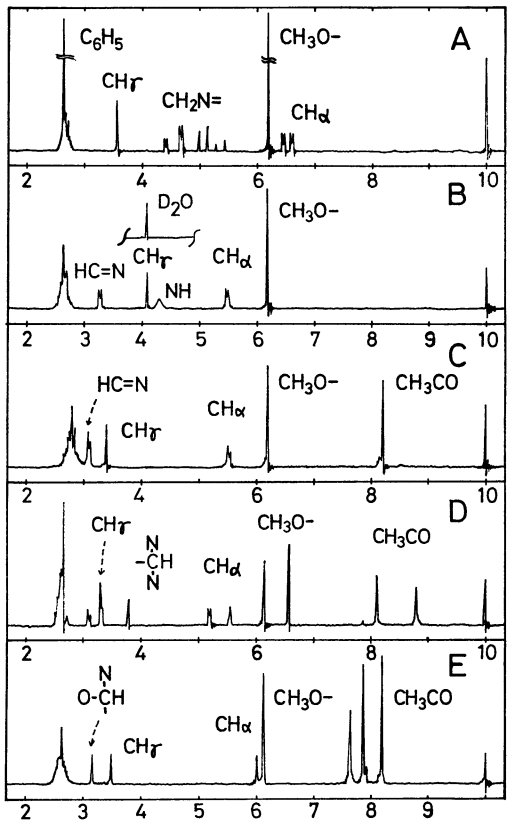


Fig. 2. NMR spectra of methyl γ-phenyl-α,β-(1-pyrazolino)paraconate (A), methyl γ-phenyl-α,β-(2-pyrazolino)paraconate (B), *N*-acetyl-2-pyrazoline **10** (C), Dimer of **10** (D), and the compound **13** (E).

10) R. Huisgen, R. Grashey and J. Sauer, "The Chemistry of Alkenes," John Wiley and Sons, Inc., New York N. Y., (1964), p. 826.

11) W. M. Jones, *J. Amer. Chem. Soc.*, **81**, 5153 (1959).

12) Acid-catalysed isomerization of 1-pyrazoline to 2-pyrazoline has been attempted: K. von Auwers and F. König, *Ann. Chem.*, **496**, 27, 252 (1932).

Table 1.

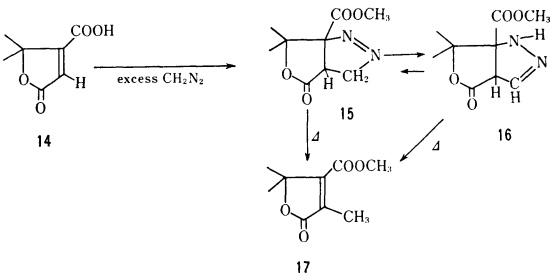
Compd.	Mp°C, (Bp °C/mmHg)	Formula	Calcd, %			Found, %		
			C	H	N	C	H	N
4	142—143.5	$C_{11}H_8O_4$	64.71	3.95	—	64.88	3.96	—
5	141.8 (decomp)	$C_{13}H_{12}N_2O_4$	60.00	4.66	10.76	60.26	4.82	10.59
6	(120/0.001)	$C_{13}H_{12}O_4$	67.23	5.21	—	66.88	5.28	—
7	143 (decomp)	$C_{25}H_{20}N_2O_4$	72.80	4.89	6.79	72.72	4.82	6.71
8	a	$C_{25}H_{20}O_4$	78.11	5.24	—	77.95	5.33	—
10	189	$C_{15}H_{14}N_2O_4$	59.60	4.67	9.27	59.90	4.92	8.98
11	218.5—220.5	$C_{30}H_{28}N_4O_{10}$	59.60	4.67	9.27	59.94	4.79	9.04
12	106	$C_{13}H_{12}N_2O_4$	60.00	4.65	10.76	59.81	4.59	10.89
13	185.5	$C_{19}H_{20}N_2O_8$	56.44	4.99	6.93	56.36	5.02	6.79
15	50.5—51.5	$C_9H_{12}N_2O_4$	50.94	5.70	—	50.63	5.72	—
16	b	$C_9H_{12}N_2O_4$	50.94	5.70	13.45	50.43	5.45	12.45
17	b	$C_9H_{12}O_4$	58.69	6.57	—	58.61	6.99	—

a) Purification was performed by column chromatography (see Experimental).
b) Separation and purification were carried out by preparative vpc.

to the diazo group[8a,13] of **5** a new band at 3360 cm^{-1} (ν_{NH}) was observed. Concerning the ester carbonyl of **12** the hydrogen bonding of the imino group may cause a shift of the absorption band from 1755 to 1725 cm^{-1}.

A mixture of 1-pyrazoline **5** and acetic anhydride in the presence of *p*-toluenesulfonic acid, on standing at room temperature for 24 hr, gave three compounds (**10**, **11**, and **13**) with a ratio of 90 : 7 : 3, respectively, whereas 2-pyrazoline **12** in the same treatment gave **13** exclusively. An attempt to prepare similar derivatives using acetic anhydride, upon standing for 2 days at room temperature, was unsuccessful.[13b,14]

The structural assignments of **10**, **11** and **13** were based on spectral and microanalytical data. The infrared spectrum of **10** shows a normal absorption band at 1742 cm^{-1} consistent with ester carbonyl owing to the loss of the hydrogen-bridge with the imino group observed on **12**. The NMR spectrum of **10** reveals that the proton at γ-position of the lactone ring is affected with the deshielding effect of acetyl carbonyl as shown in Fig. 2. Similarly, the NMR spectrum of **13** (Fig. 2) indicates that the deshielding effect of the neighbouring *N*-acetyl group is also expected to affect the hydrogen atom attached to the C_3 carbon atom and causes a pronounced shift to the lower field, while the shielding effect of the acetoxy group shifts the signal of the CH_α proton upfield. A structure of **11** for one of the minor products, mp 218—220°C, 7% of yield, consistent with the spectral and microanalytical evidences (See Table 1), is considered tentatively as a dimer of **5**. The infrared spectrum of **11** (Fig. 1) is subequal to that of **5**. The NMR spectrum of **5** shows a complex pattern, but number of the whole protons appearing in the chart of Fig. 2 coincides exactly with that of **11**.



Scheme III

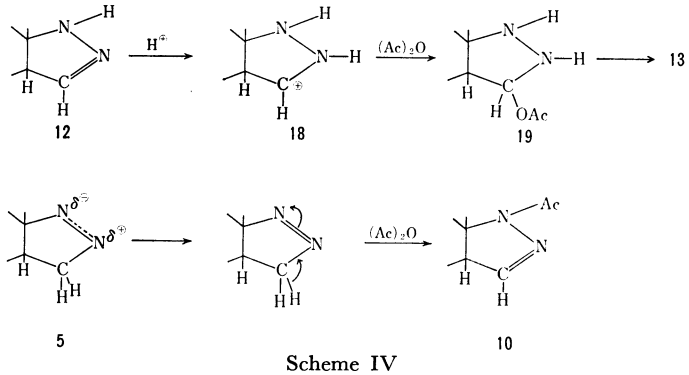
The thermochemical stability about the tautomers (**15** and **16**) was found to be structure dependent when examined by vpc, since most of **15** was converted into **17** smoothly, whereas about 20% of change for **16** was noted as indicated in Table 2. It seems that the conversion of **16** into **17** may proceed *via* 1-pyrazoline **15**.[15] The partial change from **15** to **16** occurred spontaneously during storage.

As illustrated in Scheme IV, a mechanistic consideration of the formation of **10** and **13** involves the assumption that **12** is first protonated and then followed by combination with anionic acetoxy group to give **19**, which leads to **13** by further *N*-acetylation. On the other hand, the formation of **10** seems to result from a direct attack of cationic acetyl group on **5** owing to the weak polarization

13) a) C. G. Overberger, J.-P. Anselme and J. R. Hall, *J. Amer. Chem. Soc.*, **85**, 2752 (1963); b) C. G. Overberger and J.-P. Anselme, *ibid.*, **86**, 658 (1964); c) C. G. Overberger, N. Weinshenker and J.-P. Anselme, *ibid.*, **87**, 4119 (1965).

14) C. G. Overberger and J.-P. Anselme, *ibid.*, **84**, 869 (1962).

15) W. M. Jones, *ibid.*, **80**, 6687 (1958).



Scheme IV

of the azo bond. In the course of the reaction from **12** to **18** the dimer **11** may be obtained by addition of **12** with the cation intermediate **18**.

Table 2

Compound		Product, yield (%)		
		15	**16**	**17**
A	**15**	0	10	90
	16	0	80	20
B	**15**	40	60	0

A: Passing on vpc column, SE-30, 3 m long at 160°C;
B: Standing for 1 month at room temperature.

Experimental[16]

Preparation of γ-Phenylaconic Acid 4. To a suspension of α-benzylidenesuccinic acid[5] and 50 m*l* of water 6.3 m*l* of bromine was added with stirring for 2 hr at room temperature and then stirred for an additional 10 hr. After the precipitate was filtered the crude solid was allowed to react with boiling water. From the aqueous layer separated by decantation, after cooling to room temperature, the precipitates were collected and recrystallized from benzene giving 12.7 g (64% based on the dicarboxylic acid) of **4**, mp 142—143.5°C; IR (Nujol) 3300—2400 (COOH), 1733 (lactone C=O), 1700 (COOH, shoulder), 1645 (C=C), 1220, 990 and 690 cm^{-1}.

β-Benzoylpropionic Acid 9 from 4. A solution of **4** (1 g) in 50 m*l* of 0.1N ethanolic sodium hydroxide solution was allowed to stand for 0.5 hr. After acidification of the alkaline solution with dilute sulfuric acid, β-benzoylpropionic acid **9** was obtained in a quantitative yield. The IR spectrum of **9** was identical with that of the authentic sample;[7] IR 1710 (acid C=O), 1675 (ketone C=O) cm^{-1}.

Methyl γ-Phenyl-α,β-(1-pyrazolino)paraconate 5. To an ethereal solution of **4** (1 g) excess diazomethane solution was added. After standing for 10 min removal of the solvent gave **5** in a quantitative yield, which on crystallization from benzene-*n*-hexane melted at 141.8°C; IR (Nujol) 1792 (lactone C=O), 1755 (ester C=O), 1553 (-N=N-) cm^{-1}; UV λ_{max}^{EtOH} 324 mμ (ε_{max} 298) and 289 mμ (ε_{max} 270)[13c]; NMR ($CDCl_3$) τ 2.62 (5H s, C_6H_5), 3.58 (1H s, CHγ), 4.64 and 5.61 (2H each q, C-CH_aH_b-N=N, J_{AB}=18.0, J_{AC}=8.7, J_{BC}=2.3 Hz), 6.19 (3H s, $-OCH_3$), 6.54 (1H q, CH_c-C-N=N).

Thermal Decomposition of 5. Pyrolytic decomposition of **5** was carried out by heating at 145—150°C for 30 min. Distillation of the residue afforded 1.6 g (*ca.* 90%) of methyl α-methyl-γ-phenylaconate **6**, bp 120°C/0.001 mmHg; IR 1766 (lactone C=O), 1725 (ester C=O), 1665 (C=C) cm^{-1}; UV λ_{max}^{EtOH} 217 mμ (ε_{max} 15000); NMR ($CDCl_3$) τ 7.77 (3H d, CH_3), 6.35 (3H s, $-OCH_3$), 4.05 (1H q, CH_γ), 2.78 (5H m, C_6H_5). A long range coupling (J=1.9—2.0 Hz) between methyl protons at α-position and a proton at γ-position was observed.

Benzyl γ-Phenyl-α,β-(3-phenyl-1-pyrazolino)paraconate 7. To an ethereal solution of **4** (1 g) excess phenyldiazomethane solution,[9] prepared from the oxidation of an ethereal solution of benzaldehydrazone with silver oxide, was added. After standing for 30 min the solid precipitated was filtered and recrystallized from benzene giving 1.7 g (88%) of **7**, mp 143°C (decomp); IR (Nujol) 1785 (lactone C=O), 1755 (ester C=O), 1553 (-N=N-) cm^{-1}; NMR ($CDCl_3$) τ 6.57 (1H d, CH_α), 4.78 (2H d, O-CH_2-Ph), 4.78 (1H d, CH-Ph), 3.67 (1H s, CH_γ), 2.70 (15H m, C_6H_5).

Thermal Decomposition of 7. Decomposition of **7** at 145—155°C for 30 min gave **8** in good yield. Purification of the crude product of **8** was performed on column chromatograph with Wako Gel-C200 using benzene-acetone-*n*-hexane (8 : 1 : 1.5) as an elute; IR 1785 (lactone C=O), 1725 (conjugated ester C=O), 1670 (C=C shoulder) cm^{-1}; UV λ_{max}^{EtOH} 225 mμ (ε 6600), NMR ($CDCl_3$) τ 6.97 and 7.20 (2H d, CH_AH_BPh J_{AB}=5.4 Hz), 5.10 and 5.21 (2H d, OCH_AH_BPh J_{AB}=7.8 Hz) 3.91 (1H s, CH_γ), 2.87 (15H m, C_6H_5).

Isomerization of 5. A mixture of **5** (0.5 g) and 20 m*l* of phosphoric acid was heated slowly with stirring for 10—15 min at 70—80°C. Upon cooling to room temperature, the reaction mixture was diluted with 50 m*l* of water and then the organic layer was taken up in ether. The extracts were washed with aqueous sodium chloride, next with saturated sodium bicarbonate solution and finally with sodium chloride solution, and

16) All melting and boiling points are uncorrected. Infrared spectra were determined with a Hitachi EPI-S2 and ultraviolet spectra on a Hitachi EPS-3T spectrophotometer. NMR spectra were obtained on a Japan Electron Optics Laboratory spectrometer (JNM-C-60) in deuteriochloroform with TMS as internal standard. Microanalyses were performed by Mr. E. Amano of the Department of Synthetics Chemistry in this Faculty and the results are listed in Table 1.

dried on Na_2SO_4. Removal of the solvent gave 0.4 g (80%) of 2-pyrazoline **12**, mp 106°C; IR (Nujol) 3360 (>NH), 1793 (lactone C=O), 1725 (ester C=O), 1600 (-C=N-) cm^{-1}; NMR ($CDCl_3$) τ 6.17 (3H s, $-OCH_3$), 5.52 (1H d, CH_α), 4.33 (1H broad, >NH), 4.09 (1H s, CH_γ), 3.27 (1H d, N=CH-), 2.68 (5H m, C_6H_5).

Acetylation of 1-Pyrazoline 5. A mixture of **5** (1 g) and 10 m*l* of acetic anhydride in the presence of a small amount of *p*-toluenesulfonic acid was kept for 24 hr at room temperature. After the reaction mixture was diluted with 20 m*l* of water and neutralized with solid sodium bicarbonate to pH 8, the organic layer was extracted with ether. The extracts were washed with saturated sodium chloride solution and dried on Na_2SO_4. Removal of the solvent gave 1 g of crude crystals which were allowed to dissolve in a hot solution of benzene-*n*-hexane (1 : 1), then standing for several hours, to give **10**. The filtrate, when allowed to stand for another day, gave **11**. After the filtrate was concentrated, 3 m*l* of hot benzene-*n*-hexane (2 : 3) was added. On cooling to room temperature, **13** was precipitated. Total yield of **10**, **11**, and **13** was in the ratio of 90 : 7 : 3. The ultraviolet spectrum of **11** showed two absorption bands at λ_{max}^{EtOH} 258 mμ (ε 5200) and 407 mμ (ε 240), whereas that of **10** showed an absorption at λ_{max}^{EtOH} 246 mμ (ε 7600). The infrared and NMR charts of these compounds (**10**, **11**, and **13**) are illustrated in Figs. 1 and 2. The physical constants together with microanalytical results are indicated in Table 1.

Acetylation of 12. Acetylation of **12** (0.2 g) was carried out in a similar manner as for **5**. After the usual treatment, 0.2 g of **13** was obtained.

Preparation of 15. To an ethereal solution of γ,γ-dimethylaconic acid **14**[17] excess diazomethane solution was added. After standing for 30 min, removal of the solvent gave **15** in a quantitative yield which melted at 50.5—51.5°C; IR (Nujol) 1775 (lactone C=O), 1735 (ester C=O) and 1558 (N=N) cm^{-1}; UV λ_{max}^{EtOH} 328 mμ (ε 210); NMR ($CDCl_3$) τ 4.72 and 5.24 (2H each q, C-CH_aH_b-N=N, J_{AB}=18.0, J_{AC}=8.0, J_{BC}=1.5 Hz), 6.12 (3H s, $-OCH_3$), 6.36 (1H q, CH_c-C-N=N), 8.40 and 8.09 (6H each s, gem CH_3).

Thermal Isomerization of 1-Pyrazoline 15 and 2-Pyrazoline 16 on VPC Column. When **15** was passed on 10% Diasolid-L Silicone (SE-30) coated column with a 3 m long, carrier gas H_2, 20 m*l*/min, operating at 160°C, two peaks of **17** and **16** were observed in a ratio of 9 : 1 (Rt: 5 and 17 min, respectively). Each component was isolated by VPC preparatively. On the other hand, the purified **16**, when passed on the same column in the similar condition, gave two peaks of **16** and **17** in a ratio of 4 : 1. These data are indicated in Table 2. The microanalyses of both **15** and **16** are recorded in Table 1. The spectral data are as follows: methyl γ,γ-dimethyl-α,β-(2-pyrazolino)-paraconate **16**, IR 3320 (NH), 1770 (lactone C=O), 1736 (ester C=O), 1588 (C=N-) cm^{-1}; NMR ($CDCl_3$) τ 8.57 and 8.40 (6H s, $-CH_3$), 6.16 (3H s, $-OCH_3$), 5.43 (1H d, CH_α J=2.6 Hz), 3.24 (1H, broad, CH=N), 2.5—4.0 (1H broad, NH); methyl γ,γ-dimethyl-α-methylaconate **17**, IR 1765 (lactone C=O), 1724 (conjugated ester C=O), 1661 (C=C) cm^{-1}; NMR ($CDCl_3$) τ 8.40 (6H s, $-CH_3$), 7.28 (3H s, α-CH_3), 6.07 (3H s, $-OCH_3$).

The authors wish to express their thanks to Professor Akira Takeda, Department of Synthetics Chemistry, for helpful discussions and encouragement.

17) R. Fittig and B. Frost, *Ann. Chem.*, **226**, 370 (1884).